Title
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Journal
The Journal of investigative dermatology, 132(3 Pt 2)

ISSN
0022-202X

Author
Modlin, Robert L

Publication Date
2012-03-01

DOI
10.1038/jid.2011.373

Peer reviewed

HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2012 September 01.

Published in final edited form as:

J Invest Dermatol. 2012 March ; 132(3 0 2): 882–886. doi:10.1038/jid.2011.373.

Innate Immunity: Ignored for decades, but not forgotten

Robert L. Modlin[1,2]

[1]Division of Dermatology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095

[2]Department of Microbiology, Immunology and Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095

Abstract

The innate immune system must recognize and rapidly respond to microbial pathogens, providing a first line of host defense. This is accomplished through an array of pattern recognition receptors (PRRs) which reside in specific subcellular compartments and can bind pathogen-associated molecular patterns (PAMPs). PRRs also recognize self-molecules that are released after cell damage or death known as danger-associated molecular patterns (DAMPs), which can be actively transported across cell membranes. The activation of PRRs leads to host defense pathways in infectious diseases but can also contribute to tissue injury in autoimmune diseases. The identification of these pathways has provided new insight into mechanisms of vaccination and holds promise for developing better vaccines. Finally, the identification of PRRs, their ligands and signaling pathways provides an opportunity for developing new immunotherapeutic approaches to skin conditions in which activation of the innate immune response contributes to disease pathogenesis.

The current model of innate immunity derives from the seminal observations of Elie Metchnikoff (Modlin and Cheng, 2004). By studying starfish larvae, he realized that mobile cells might serve in the host's defense against microbial pathogens. In 1884, Metchnikoff demonstrated that cells of the water-flea *Daphnia*, which he termed phagocytes, were attracted to and engulfed spores of a yeast-like fungus (Metschnikoff, 1884). He wrote that “the spores which reached the body cavity are attacked by blood cells, and- probably through some sort of secretion- are killed and destroyed”. Thus Metchnikoff had described the direct functions of the innate immune system: 1) rapid detection of microbes, 2) phagocytosis and 3) antimicrobial activity. The phagocytic function of the innate immune system also contributes to tissue homeostasis, for example in clearing toxic metabolites, dead cells and debris, as well as in regulating wound healing.

The contemporary view of the innate immune system is based on Metchnikoff's model. The direct functions of the innate immune system provide a rapid first line of defense against microbial pathogens. However, the innate immune system by itself may not be sufficient to

Address correspondence to: Robert L. Modlin, M.D., UCLA Division of Dermatology, 52-121 CHS, 10833 Le Conte Avenue, Los Angeles, CA 90095, Tel: (310) 825-6214, Fax: (310) 206-9878, rmodlin@mednet.ucla.edu.

eliminate many microbial pathogens. Ultimately, the adaptive immune system, composed of T and B cell, and although slower to develop than the innate immune response, clears the microbial invader. The innate and adaptive immune responses are linked, as the innate immune response has an indirect function in host immunity, an instructive role in stimulating adaptive T and B cell responses. Conversely, the adaptive immune response can activate cells of the innate immune system.

It would take over 100 years after Metchnikoff's description of innate immunity for immunologists to discover the mechanisms by which cells of the innate immune system could rapidly recognize microbial invaders and subsequently destroy them. Improvements in light microscopy provided Metchnikoff with the necessary scientific tool to discover innate immunity. In 1868, the microscope allowed Paul Langerhans to visualize cells with a dendritic morphology in the epidermis (Langerhans, 1868). These cells, known as “Langerhans cells”, are now known to be a key part of the skin immune system.

In 1873, Gerhard Armauer Hansen used microscopy to discover the first human pathogen, *Mycobacterium leprae*, the cause of leprosy (Hansen, 1874). Fehleisen identified and cultured *Streptococcus pyogenes* as the causative agent of erysipelas (Fehleisen, 1883). Around this time, several investigators noted that the occurrence of erysipelas in cancer patients sometimes resulted in the regression or remission of the tumor, including Busch (Busch, 1866), Fehleisen (Fehleisen, 1883) and the Russian writer and physician, Anton Chekov (Gresser, 1987). In addition, patients with various malignancies were inoculated with “erysipelas” and shrinkage of the tumor was noted (Fehleisen, 1883). William B. Coley continued these studies, and reported in 1891 that in patients with sarcoma, there was regression of the tumor upon contraction of erysipelas (Coley, 1891). Coley directly inoculated ten patients with various sarcomas with a bacterial culture derived from erysipelas lesions, as well as the toxins from these cultures, resulting in dramatic regression of some tumors (Coley, 1893). These “Coley's toxins” were a mixture of *Streptococcus pyogenes* and *Serratia marcescens*. Coley is frequently labeled as the “father of immunotherapy”, and the mechanism of such therapy involving activation of the innate immune system. It is also worth considering why a skin disease, erysipelas, was identified as a potential mechanism of augmenting anti-tumor immunity. Clearly the skin is readily observable and accessible, so it was more likely that an exact clinical diagnosis based on morphology could be made and that specimens could be readily obtained for microbiologic identification or immunotherapy. It is therefore no accident that some of the early breakthroughs in microbiology and immunotherapy came from the study of skin diseases such as leprosy and erysipelas.

As scientists were trying to improve vaccines, they noted that an intercurrent infection enhanced efficacy. Lewis and Loomis: “were led by an accidental occurrence to carry through an experiment designed to show whether a preexisting tuberculosis affected the production of antibody for an antigen unrelated to the tubercle bacillus. The result was definite, showing a decided increase in anti-sheep amboceptor production by tuberculous guinea pigs.”(Lewis and Loomis, 1924) They called this ability of tuberculosis infection to increase anti-sheep erythrocyte antibody production “allergic irritability”. In modern

immunology, we describe this as an adjuvant, an agent that when added to a vaccine would augment the immune response to the target antigen.

The term adjuvant, from a Latin word meaning ‘to help’, was coined in the 1920s by Gason Ramon, a veterinarian at the Pasteur Institute (Pollack, 2009). He found that horses immunized with diphtheria toxoid have a stronger response if they developed an abscess at the inoculation site, and that adjuvant activity was obtained by the addition of substances such as bread crumbs or tapioca to the vaccine (Ramon, 1925; Ramon, 1926). At the same time, aluminum salts were used to precipitate and purify toxins, as well as in immunization protocols. Importantly, the efficacy of a diphtheria toxoid vaccine was improved by the addition of alum (Glenny et al., 1926), which subsequently became a major adjuvant in vaccines against infections in humans. In 1956, Freund developed what would become the standard adjuvants for vaccines in animal studies (Freund, 1956). Freund's complete adjuvant utilizes inactivated mycobacteria as a component. Subsequently, the immunotherapeutic potential of the live mycobacterium BCG was explored in bladder cancer (Morales et al., 1976) and melanoma (Morton et al., 1970).

For over a century, immunologists used bacterial products in vaccines, with the knowledge that bacterial products had special properties that could be harnessed in preventing and treating disease, yet unaware of the mechanisms involved. Discovery of the molecular mechanisms of innate immunity and how adjuvants work would require over 100 years of scientific and technical progress in a variety of disciplines: cell biology, biochemistry, genetics and high speed computing. Innate immunity was ignored, but not forgotten; it was not understood, but it was induced as part of vaccines.

Charles Janeway advanced our thinking about the mammalian innate immune system by confronting what had been ignored, asking “Why do we need to use adjuvants” (Janeway, Jr., 1989). It was necessary to add adjuvants to vaccines in order to induce robust immune responses to antigen. Janeway called this “the immunologists dirty little secret” (Janeway, Jr., 1989). He further reasoned that the adaptive immune response required two signals for activation: ligation of the specific receptor on the surface of a T or B cell by the antigen, but also a second signal derived from another cell, the antigen presenting cell, later identified as costimulatory molecules (Janeway, Jr., 1989). Janeway hypothesized that the capacity of antigen presenting cells to elicit an adaptive response was induced by a distinctive recognition event involving evolutionarily primitive receptors, enhancing antigen presentation function. Janeway's group gained insight from the study of innate immunity in *Drosophila*, implicating the Toll protein in recognition of foreign microbes and in activating host defense. They discovered that triggering of a human homolog of the *Drosophila* Toll protein, Toll-like receptor 4 (TLR4), on innate immune cells, upregulated costimulatory molecule expression and cytokine release required for T cell activation (Medzhitov et al., 1997). These data indicated that activation of TLRs on cells of the innate immune system could instruct the adaptive immune response.

The discovery that TLRs could trigger innate immune responses raised the possibility that TLRs mediated recognition of microbial ligands. It was known that the innate immune system detected microbes using pattern recognition receptors, which recognized biochemical

patterns expressed by groups of microbes, termed pathogen-associated molecular patterns (PAMPs). Yet up until that time, many of the identified pattern recognition receptors (PRRs) had no known intracellular signaling capacity. TLRs were logical candidates- being transmembrane proteins containing repeated leucine-rich motifs in their extracellular portions, similar to other pattern recognition proteins and containing a cytoplasmic portion which is homologous to the IL-1 receptor, and hence could trigger intracellular signaling pathways. Beutler's group used a genetics approach to identify TLR4 as the receptor for LPS, providing a mechanism for innate immune recognition of Gram negative bacteria (Poltorak et al., 1998). Our lab discovered that microbial lipoproteins trigger host responses via TLR2, providing a mechanism for innate immune recognition of both Gram positive and Gram negative organisms. TLR2/6 heterodimers mediate the response to diacylated lipoproteins, whereas TLR2/1 heterodimers recognize triacylated lipoproteins (Brightbill et al., 1999). For recognition of bacteria, the TLR system is redundant: TLR9 is activated by unmethylated DNA sequences (CpG dinucleotides) found in bacterial DNA (Hemmi et al., 2000) and TLR5 activated by bacterial flagellin (Hayashi et al., 2001). Specific TLRs are involved in viral recognition: TLR3 is activated by viral derived double-stranded RNA (Alexopoulou et al., 2001) and TLR7 and TLR8 by viral derived single stranded RNA (Diebold et al., 2004) (Figure 1).

The identification of TLR ligands made possible experiments to investigate the functional role of TLRs in the innate immune response. In Metchnikoff's model of innate immunity, recognition of the foreign invader was followed by phagocytosis. It is required not only for physical destruction of the pathogen, but also allows for microbial antigen presentation to T cells in the context of MHC molecules. TLRs can regulate phagocytosis either through enhancing endosomal fusion with the lysosomal compartment (Blander and Medzhitov, 2004) or through induction of a phagocytic gene program including multiple scavenger receptors (Doyle et al., 2004).

TLRs also fulfill the final step of Metchnikoff's innate immunity- the induction of direct antimicrobial activity. Activation of TLRs on monocytes triggers an antimicrobial activity against intracellular bacteria such as *M. tuberculosis*, which in mice is NO dependent and human NO independent (Thoma-Uszynski et al., 2001). In human monocytes, activation of TLRs induced an antimicrobial activity against *M. tuberculosis* that was vitamin D dependent (Liu et al., 2006). This pathway involved induction of IL-15, leading to induction of 25-hydroxyvitamin D3-1α-hydroxylase (CYP27b1), which converts 25D into the active 1,25D form and upregulation/ activation of the vitamin D receptor (VDR) (Krutzik et al., 2008). The activation of the VDR triggered expression of the antimicrobial peptide cathelicidin (Liu et al., 2006). Furthermore, the induction of IL-1β and the VDR was required for upregulation of DEFB4 (Liu et al., 2009). The TLR-induced, vitamin D-dependent antimicrobial pathway required induction of the antimicrobial peptides cathelicidin and DEFB4 (Liu et al., 2007). In addition, activation of TLR3, TLR4, TLR7, TLR8 and TLR9 leads to induction of antiviral activity that is dependent on Type I interferon secretion and involves specific signaling pathways (Doyle et al., 2002).

The specific subcellular location of TLRs allows the detection of microbes in distinct compartments. TLR3, 7, 8 and 9 are located in endosomes, facilitating recognition of RNA

and DNA from microbial pathogens that reside in the endocytic pathway. In contrast, TLR1, 2, 4, 5 and 6 are located on the cell surface, providing the innate immune system with the ability to recognize extracellular pathogens or PAMPs released from intracellular pathogens into the extracellular space. Other PRRs are located in the cytoplasm, including the NLRs (NOD [Nucleotide-binding oligomerization domain]-like receptors), which share homology to TLRs in containing leucine rich repeats. NOD1 and NOD2 recognize components of bacterial cells walls; specifically NOD1 recognizes D-glutamyl-meso-diaminopimelic acid (Girardin et al., 2003a) and NOD2 senses muramyl dipeptide (Girardin et al., 2003b; Inohara et al., 2003; Yang et al., 2007). Stimulation of NLRs can activate a protein complex known as the inflammasome, which by recruitment of caspase-1, leads to the proteolytic cleavage and activation of IL-1β and other cytokines (Martinon et al., 2009).

The discovery of NLRs has provided new insight into how vaccine adjuvants work. It is tempting to speculate that the utility of BCG as an adjuvant is related to its ability to activate NOD2. A key component of mycobacterial cell walls that confers adjuvant activity is the NOD2 agonist, muramyl dipeptide (Adam et al., 1974; Ellouz et al., 1974). Muramyl dipeptide has been shown to be an effective adjuvant for inducing both B cell (Specter et al., 1978) and T cell (Sugimoto et al., 1978) responses. A muramyl dipeptide derivative has been explored as a possible immunotherapeutic agent in the treatment of patients with osteosarcoma (Kleinerman et al., 1992). Human monocytes with a functional defect in NOD2 were found to have an 80% reduction in cytokine response to *M. tuberculosis* (Ferwerda et al., 2005). The vaccine adjuvant alum also activates the NLR family, specifically the inflammasome component Nalp3 (Eisenbarth et al., 2008).

In addition to recognizing pathogen associated molecular patterns (PAMPs) derived from microbes, pattern recognition receptors of the innate immune system have been able to recognize danger associated molecular patterns (DAMPs) derived from injured or damaged host cells (Martinon et al., 2006). Some DAMPs include ATP, heparin sulfate, HMGB1 and S100 proteins. The ability of the innate immune response to respond to DAMPs contributes to tissue homeostasis and repair, but the resulting inflammatory response can result in autoimmune disease. For example, the recognition of uric acid crystals by the NALP3 inflammasome contributes to the pathogenesis of gout (Martinon et al., 2006). Of relevance to skin disease, the inflammasome is activated in keratinocytes by UVB, as well as chemical agents that induce irritant and contact dermatitis (Watanabe et al., 2007).

The location of pattern recognition receptors of the innate immune system in distinct subcellular compartments facilitates detection of microbial pathogens. At the same time, the location of these receptors prevents activation by self-molecules which share homology to microbial ligands, but do not normally access these locations. However, when self-molecules gain access to these compartments, autoimmune disease can be triggered (Davis et al., 2011; Martinon et al., 2009). The innate system participates in inflammation associated carcinogenesis (Davis et al., 2011). In the case of cell damage or death, the upregulation and release of DAMPs provides one mechanism by which self-molecules gain access to innate immune pattern recognition receptors. A second mechanism involves the transport of self-molecules across membranes into compartments containing specific pattern recognition receptors.

Michel Gilliet's group has elucidated a transport mechanism by which self-DNA is trafficked from an extracellular location directly to endosomes resulting in activation of the innate immune system via TLR9 (Lande et al., 2007). This transportation pathway may contribute to the pathogenesis of psoriasis. First, the release of DNA from damaged cells complexes with the antimicrobial peptide cathelicidin (aka LL-37), known to be increased in psoriasis. These DNA-cathelicidin complexes can then be transported across cell membranes and then delivered into endosomes of plasmacytoid dendritic cells, with subsequent activation of TLR9 and release of type I IFNs known to trigger autoimmune T cell responses. Cathelicidin and anti-DNA/RNA antibodies can transport both DNA and RNA into endosomes where they activate relevant TLRs and contribute to the pathogenesis of autoimmune disease. These transportation pathways may be beneficial to the host in combating microbial infection, but can also contribute to tissue damage.

There are a wide range of inflammatory and infectious skin diseases in which activation and/or dysregulation of pattern recognition receptor signaling contributes to pathogenesis (Lai and Gallo, 2008; Terhorst et al., 2010). The discovery of mammalian pattern recognition receptors and their biologic roles has also provided an exciting new opportunity to develop new pharmacologic agents. We have learned from the study of innate immunity that the drug imiquimod, used to treat viral warts and actinic keratoses, triggers TLR7 to induce a pro-inflammatory response (Hemmi et al., 2002). It is tempting to speculate that other TLR and NLR agonists may also serve as immunotherapeutic agents and/or adjuvants for a new generation of vaccines. However, there are circumstances in which blocking innate immune responses may be beneficial, raising the possibility that antagonists hold promise for a new class of anti-inflammatory agents. Metchnikoff's initial studies of the innate immune systems of starfish and the water-flea have enabled us to develop insight into the human innate immune system and provide the potential to intervene in human disease.

Acknowledgments

I am grateful to Mirjam Schenk for insightful comments. Supported by NIH grants R01 AR40312, R01 AI022553, R01 AI047868 and R01 AI073539.

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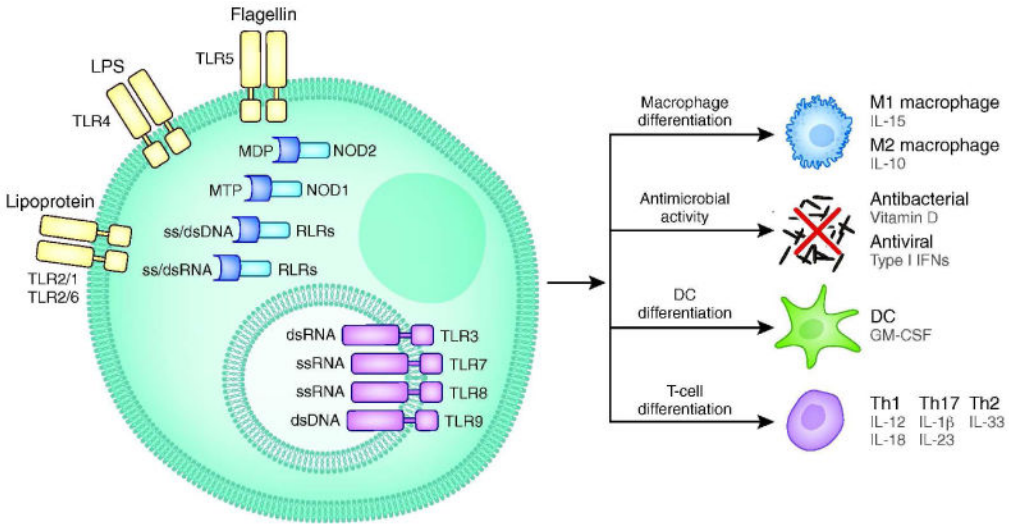

Figure 1. Innate immune pathways of host defense in infection

Innate immune receptors reside in specific subcellular compartments, including cell surface, cytoplasmic and endocytic, providing the opportunity to recognize distinct microbial ligands. Some of the key pattern recognition receptors (PRRs) involved in skin disease are shown, along with some of their microbial ligands, pathogen-associated molecular patterns (PAMPs). Included are various TLRs (Toll-like receptors), NLRs (NOD-like receptors), RLRs (RIG-I like receptors). The activation of the innate immune system leads host immune responses that contribute to skin disease including the differentiation of monocytes into macrophage subsets, antimicrobial activity, dendritic cell differentiation and T cell differentiation. The key molecules involved in each process are shown.